REMARKS

Applicants have amended Figure 1 to correct a typographical error. In particular, applicants have amended sheet 35 of Figure 1 to change the residue identifier for residue 331 (atoms 1984-1989) to "CYS." Support for this amendment can be found throughout the specification, for example, on page 49, lines 1-3. For clarification, applicants have also changed the residue number for IMP (atoms 1990-2012) to "A1331."

Applicants have amended claims 23, 29, 32, 35 to recite a method for selecting a chemical entity that associates with an IMPDH binding pocket, or homologue thereof, with a quantified deformation energy of not greater than about 10 kcal/mole. Support for this amendment, which clarifies but does not narrow the scope of the claim, can be found throughout the specification, for example, on page 27, line 10 to page 30, line 16; and page 32, line 32 to page 34, line 9. In addition, applicants have deleted the phrase "wherein said docking utilizes energy minimization" from these claims.

Applicants have amended claims 23 and 27-34 to recite a method for selecting a chemical entity comprising the step of determining structure coordinates of IMDPH amino acids to characterize a binding pocket. Applicants have also amended claims 27, 28, 30, 31, 33, and 34 to be independent claims. Support for these amendments, which do not narrow the scope of the claims, can be found throughout the specification, for example, at page 12, lines 11-26; and page 16, line 3 to page 19, line 5.

Applicants have amended claim 35 to recite the steps of producing a crystal and determining the three-dimensional structure of the molecule or molecular complex; employing computational means to dock a chemical entity to the molecule, molecular complex, or homologue thereof; quantifying the deformation energy of binding; outputting the deformation energy; and selecting the chemical entity based on the deformation energy. Support for this amendment can be found throughout the specification, for example, at page 24, lines 13-21; page 27, line 10 to page 29, line 21; page 32, line 32 to page 34, line 32; page 39, line 30 to page 42, line 23; and Examples 1-3.

Applicants have amended claim 37 to further recite docking that is followed by energy minimization. Support for this amendment can be found in the specification at page 29, lines 7-21.

Applicants have amended claim 38 to recite a method comprising the step of selecting a chemical entity that inhibits the catalytic activity of the molecule or molecular complex. Support for this amendment, which clarifies the claim without narrowing the scope, can be found throughout the specification, for example, at page 28, line 20 to page 29, line 21; and Examples 6 and 7.

Applicants have amended claim 39, and added claims 64-71, to recite a method for selecting a chemical entity comprising the steps of producing a crystal, determining the three-dimensional structure coordinates of a molecule or molecular complex, and employing computational means to utilize all or part of a binding pocket characterized by structure coordinates of a set of IMPDH amino acids as well as to recite the steps in amended claims 23 and 27-34. Support for this amendment can be

found throughout the specification, for example, at page 14, line 1 to page 19, line 5; page 39, line 30 to page 42, line 23; Examples 1-3; and Figure 1.

Applicants have amended claim 40 to recite that the docking step includes a visual inspection step. Support for this amendment can be found throughout the specification, for example, at page 26, lines 20-28; and page 29, lines 7-21.

Applicants have amended withdrawn claims 41, 44, 47, and 50 to recite that a second chemical entity may associate with a homologue of a binding pocket of interest. Applicants have also amended claims 41, 44 and 47 to change their dependencies. Support for these amendments can be found throughout the specification, for example, at page 11, lines 15-28; page 12, lines 1-10; page 14, lines 1-14; and page 15, line 26 to page 19, line 5.

Applicants have added claim 63 to recite a method according to any one of claims 23, 29, 32 and 35 wherein the selection of the chemical entity is based on a quantified deformation energy of binding of less than 7 kcal/mole. Support for this amendment can be found throughout the specification, for example, at page 32, line 32 to page 34, line 9.

Applicants have canceled claims 36, 42, 43, 45, 46, 48, 49, 52, 55 and 58 without prejudice. Applicants reserve the right to file for and obtain claims directed to canceled subject matter in divisional and continuing applications claiming priority and benefit herefrom.

None of these amendments adds new matter.

1. Election/Restriction

The Examiner maintains that claims 41-51 are directed to an independent and distinct invention. In particular, the Examiner states that claims 41, 44, 47, 50 and 51, although amended to depend upon elected claims 23, 29, 32 and/or 35, are not directed to methods of selecting chemical entities. The Examiner asserts that the steps added by these claims are directed to different end results, specifically, designing a compound or complex by assembling two chemical entities. The Examiner states that these methods can be shown to be distinct from the method for selecting a chemical entity based on its ability to associate with a binding pocket as each method has different method steps and/or goals and would require a non-coextensive search. Accordingly, the Examiner has withdrawn claims 41-51 from consideration, as being directed to a non-elected invention. Applicants request reconsideration.

The Manual of Patent Examining Procedure (MPEP) states that there are two criteria for proper restriction between patentably distinct inventions. The first is that the inventions must be independent or distinct, as claimed. The second is that there must be a serious burden on the Examiner, if restriction is not required. The MPEP further states that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." MPEP § 803. A search of the subject matter of claims 41-51 would not be unduly burdensome and, therefore, applicants request that the Examiner reconsider the restriction of the claims.

2. Written Description/New Matter: 35 U.S.C. § 112, first paragraph

Claims 23, 27-40, 52, 55 and 58 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed.

First, the Examiner states that, as previously amended, claims 23, 29, 32, and 35 are directed to a method for "selecting at least one of a plurality of chemical entities based on its ability to associate" and require that the docking process utilize energy minimization and that the selection process be based upon a quantified association. The Examiner contends that applicants have pointed to no basis for these amendments and that none is apparent. The Examiner further asserts that, in claims 23, 29, 32, and 35, although the preamble recites "at least one of a plurality", the body of the claims do not recite the docking of more than one chemical entity, as there are, the Examiner contends, no iterative steps and no plurality. The Examiner further contends that the basis for selection following output of the quantified association is unknown.

Applicants have deleted the phrase "wherein said docking utilizes energy minimization" from claims 23, 29 and 32. Furthermore, as noted in the Remarks *supra*, applicants have amended claims 23, 29, 32 and 35 to reflect selecting a chemical entity based on a quantified deformation energy of not greater than 10 kcal/mole. Thus, one of skill in the art would base the selection of any given chemical entity on that recited criterion.

The support for selecting a chemical entity based on its ability to associate was provided on page 19, line 19 to page 20, line 1 of the Amendment and Reply, filed on January 13, 2004. There, applicants stated that support could be found in the specification, as originally filed, at, for example, page 29, line 2 to page 30, line 16. In particular, the cited section of the specification provides literal support for using specialized computer programs to screen and select chemical entities based on their ability to associate with IMPDH-like binding pockets. See page 29, lines 2-9 of the specification. This selection process proceeds with the docking of the candidate chemical entity within the binding pocket. See page 29, lines 15-17 of the specification.

To overcome the Examiner's "preamble" objection, applicants have amended claims 23, 29, 32 and 35 to recite a method for selecting a chemical entity, as noted in the Remarks *supra*, rather than a plurality of chemical entities. This amendment is clarifying in nature and does not change the scope of the claims. Furthermore, as noted in the Remarks *supra*, applicants have amended claims 23, 29, 32 and 35 to reflect selecting a chemical entity based on a quantified deformation energy of not greater than about 10 kcal/mole. Thus, one of skill in the art would base the selection of any given chemical entity on that recited criterion.

The Examiner alleges that claim 35, as previously amended, appears to dock a chemical entity to IMPDH where XMP* and MPA are already docked. The Examiner contends that there is no basis for this recitation.

Applicants have amended claim 35 to recite a molecular complex defined by the set of structure coordinates of IMPDH and MPA or XMP*. Applicants clearly contemplate the docking of chemical entities to molecular complexes

comprising IMPDH and either MPA or XMP* on page 34, lines 10-32 of the specification as originally filed.

The Examiner states that the basis for the amendments to previously amended claim 37 are not understood. The Examiner contends that the cited page (page 29, lines 7-17) does not appear to describe the claimed method.

The Examiner has inadvertently pointed to applicants' support for claim 40, not amended claim 37. In the January 13, 2004 Amendment, applicants pointed to page 29, lines 7-21 of the specification as supporting the amendments to claim 37. Page 29, lines 17-19 of the specification describes that docking may be followed by energy minimization and molecular dynamics. Additional support for claim 37 can be found in the specification as originally filed on page 34, lines 10-17 (shape complementarity).

The Examiner states that claim 39 is new matter. In particular, the Examiner asserts that the specification does not disclose or contemplate producing other crystals having the same binding pocket coordinates as set forth in claims 23, 29, and/or 32. The Examiner states that these claims are directed to any crystal and not the one exemplified, whose structure coordinates are given in Figure 1.

Applicants have amended claim 39 to be an independent claim and to clarify that the molecule or molecular complex comprises IMPDH. This amendment merely clarifies the claim and does not narrow the claim. Claim 39, as first filed, and as amended, does not encompass any crystal, but encompasses a crystal comprising a molecule or molecular complex comprising IMPDH.

As set forth in the specification, applicants describe, and provide support for, crystallizing new molecules and molecular complexes, for example, other crystal forms of IMPDH or IMPDH complexes. See, e.g., page 39, line 24 to page 40, line 11, page 41, line 23 to page 42, line 23. Thus, other crystals of IMPDH or IMPDH complexes that comprise the recited binding pockets are part of applicants' invention. See also page 12, lines 1-10 and page 16, line 3 to page 23, line 7.

The Examiner asserts that claim 40 indicates that the fitting operation is performed through visual inspection. The Examiner states that the specification indicates that while visual inspection may be a starting point, the process must involve docking. The Examiner states that there does not appear to be basis in the specification for the use of visual techniques alone.

Pending claim 40 does indeed reflect that visual inspection is performed with docking. Nonetheless, for clarification, applicants have amended claim 40 to reflect that the docking step includes a visual inspection step. This amendment merely clarifies the claim and does not narrow its scope.

The Examiner asserts that while claims 55 and 58 are directed to methods where the quantified association is deformation energy, no basis is pointed to and none is apparent. The Examiner also contends that while page 33 discloses designing inhibitors having a particular deformation energy, the claims are not so limited.

As noted in the Remarks *supra*, applicants have canceled claims 55 and 58, thereby overcoming the rejection.

In view of the above arguments and amendments, applicants request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph, rejections of claims 23 and 27-35, and 37-40 (claims 36, 52, 55 and 58 are canceled).

3. Enablement: 35 U.S.C. § 112, first paragraph

Claims 23, 29, 32 and 35 stand rejected under 35 U.S.C. 112, first paragraph, for failing to enable one of skill in the art to make and use the claimed invention.

First, the Examiner contends that the claims do not result in the goal of their preambles. The Examiner asserts that while the preambles discuss the docking of "at least one of a plurality" the body of the claim does not dock more than one chemical entity.

As noted *supra*, applicants have amended claims 23, 29, 32 and 35 to recite the selection of a chemical entity, thereby overcoming the rejection.

Secondly, the Examiner states that the claims lack the criteria by which the selection among chemical entities is made. The Examiner contends that, with the exception of claims 55 and 58, as amended, one of ordinary skill in the art is not guided as to what type of value the claims require for quantification. The Examiner further asserts that, even for claims 55 and 58, the value required to guide one of skill in the art to select a chemical entity is not provided. The Examiner also states that the specification provides no examples using the structural coordinates of Figure 1 in the methods as claimed.

As noted *supra*, applicants have amended claims 23, 29, 32 and 35 (claims 55 and 58 have been canceled) to recite expressly that the selection of the chemical entity in question is predicated on its having a deformation energy of binding of not more than 10 kcal/mole. Thus, one of skill in the art is given a specific criterion, and therefore ample guidance, with which to practice the claimed invention.

Applicants direct the Examiner's attention to MPEP § 2164.02, which states, in pertinent part, that "[c]ompliance with the enablement requirement 35 U.S.C. 112, first paragraph does not turn on whether an example is disclosed...in other words, lack of working examples...should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." In view of the amendment, one skilled in the art of molecular modeling would be able to practice the claimed invention given the guidance of the present specification and her technical knowledge, without undue experimentation.

In view of the above arguments and amendment, applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. 112, first paragraph.

4. Indefiniteness: 35 U.S.C. § 112, second paragraph

Claims 23, 27-40, 52, 55 and 58 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention.

First, the Examiner contends that claims 23, 27-40, 52, 55 and 58 are confusing as they require selecting at least one of a plurality of chemical entities, yet

there are no repetitive or iterative steps in the body of the claims. The Examiner also contends that the claims are confusing as they do not provide any criteria by which a chemical entity is selected. Finally, the Examiner asserts that it is unclear as to how a selection is made after all of the quantified associations are output to suitable output hardware because selections are never saved or communicated in any fashion.

As discussed above, applicants have amended claims 23, 29, 32 and 35 (claims 52, 55, and 58 are canceled) to reflect the selection of a chemical entity and to include a criteria by which a chemical entity is selected. The amended claims also recite outputting a quantified deformation energy of binding to a suitable output hardware, for example, CRT display terminals, printers, and disk drives for storing system output for later use. See page 24, lines 13-21 of the specification as originally filed. The quantified deformation energy value can be displayed on a computer terminal or printed such that it can be observed by one of skill in the art, or saved on a disk drive for later use or viewing. These output devices would allow the quantified deformation energy to be communicated to one skilled in the art, enabling him to select the chemical entity.

The Examiner contends that claim 35 is confusing since it is unclear if the chemical entity is docked to the IMPDH structure where the XMP* and MPA are already docked. The Examiner contends that claims 36 is more confusing in that the complex could be limited to amino acids 1-514 of IMPDH.

As noted *supra*, amended claim 35 does recite a method of docking the chemical entity to the IMPDH structure wherein either XMP* or MPA is bound. Support for this method is discussed in Section 2, above. Applicants have canceled claim 36.

The Examiner contends that claim 38 is confusing because claims 23, 29 and 32 are not directed to molecular complexes. The Examiner also asserts that the preamble of claim 38 is not consistent with the steps of the claim. In particular, the Examiner notes that the added steps of contacting the chemical entity with the molecule or molecular complex and monitoring the catalytic activity are inconsistent with a selection. The Examiner contends that the steps appear to be directed to wet chemistry but, the Examiner asserts, the claim does not possess limitations to a physical molecule, molecular complex or chemical entity. The Examiner also contends that claim does not make clear the attribute of interest in the monitoring step.

As noted in the Remarks *supra*, applicants have amended claim 38 to recite the step of selecting the chemical entity if it inhibits the molecule's catalytic activity. Reading the claim in light of the teachings of the specification, one of skill in the art would understand that selecting the chemical entity on the basis of observed changes in the catalytic activity of the molecule would involve an assay. Therefore, the language of amended claim 38 is not ambiguous.

In view of these arguments and amendments, applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. 112, second paragraph.

5. Obviousness: 35 U.S.C. § 103(a)

Claims 23, 27-37, 40, 52, 55 and 58 stand rejected under 35 U.S.C. 103(a) as being unpatentable over N. Claude-Cohen et al. (1990) (hereafter "Claude-

Cohen"). In particular, the Examiner contends that Claude-Cohen describes computer programs and methods for docking chemical entities to a binding pocket wherein docking utilizes energy minimization, quantifying the association, outputting the results, and selecting chemical entities based on those results. The Examiner argues that Claude-Cohen also describes visual inspection by means of computer graphics. The Examiner also contends that the input for the program disclosed by Claude-Cohen is three dimensional structural information. The Examiner also states that shape complementarity and molecular dynamics are disclosed, and the calculation of deformation energy is disclosed.

The Examiner contends that the difference between the Claude-Cohen prior art and the claimed invention is just the recited three-dimensional structural information. The Examiner argues that this information is descriptive information stored on or employed by a machine where, the Examiner contends, it is fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps that do not impose a change in the processing steps. Therefore, the Examiner argues that the structure coordinates are nonfunctional descriptive material. The Examiner also contends that the claimed invention uses known software to solve a known problem in a conventional manner. The Examiner cites *In re Gulack* and the Trilateral Report (Trilateral Project WM4 Report) to support these propositions.

Claims 23, 27-35, 37 and 40, as amended, (claims 36, 52, 55 and 58 are canceled) recite a positive step whereby the practitioner determines that a set of amino acids constitutes an IMPDH binding pocket of interest for selecting a chemical entity that will associate with the binding pocket. Claude-Cohen does not teach or suggest the determination of the recited set of amino acids of an IMPDH binding

pocket for identifying chemical entities. Neither of the claims in Case 6 or 7 of the Trilateral Report recites this positive determination step.

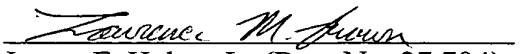
In addition, the determination step requires the intervention of the skilled practitioner and is not merely applying new data to the method steps in Claude-Cohen. The determination step is inventive because it requires that the skilled artisan apply her expertise interactively with the disclosed IMPDH structure coordinates to determine which specific set of amino acids in the IMPDH or IMPDH homologue molecule best delineate a binding pocket of interest. Furthermore, the specific set of amino acids determined are advantageous for identifying potential IMPDH inhibitors compared to other possible sets of amino acids from an IMPDH or IMPDH homologue molecule that could define the binding pocket.

Thus, amended claims 23, 27-35, 37 and 40 (claims 36, 52, 55 and 58 are canceled) are not obvious in view of Claude-Cohen. In view of the above arguments, applicants request withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

Applicants respectfully request that the Examiner reconsider and withdraw all outstanding rejections, enter the proposed amendments and added claims, and pass the claims to allowance.

Respectfully submitted,



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AMENDMENTS TO THE DRAWINGS

Please replace sheet 35 of Figure 1, as originally filed, with replacement sheet 35 submitted herewith as an Appendix.

FIGURE 1 (CONT.)

ATOM	1970	N	SER	329	67.706	70.528	87.822	1.00	23.68
ATOM	1971	CA	SER	329	67.077	69.925	89.000	1.00	22.19
ATOM	1972	CB	SER	329	68.150	69.406	89.964	1.00	19.55
ATOM	1973	OG	SER	329	69.028	70.440	90.356	1.00	23.14
ATOM	1974	C	SER	329	66.077	70.812	89.747	1.00	23.28
ATOM	1975	O	SER	329	64.978	70.362	90.065	1.00	25.72
ATOM	1976	N	ILE	330	66.444	72.070	89.992	1.00	22.81
ATOM	1977	CA	ILE	330	65.584	73.024	90.700	1.00	19.85
ATOM	1978	CB	ILE	330	66.410	74.017	91.589	1.00	15.67
ATOM	1979	CG2	ILE	330	66.509	73.500	93.001	1.00	18.25
ATOM	1980	CG1	ILE	330	67.795	74.289	90.994	1.00	7.11
ATOM	1981	CD1	ILE	330	67.776	74.921	89.639	1.00	5.46
ATOM	1982	C	ILE	330	64.703	73.869	89.786	1.00	20.60
ATOM	1983	O	ILE	330	64.225	74.923	90.201	1.00	23.53
ATOM	1984	N	IMP CYS	331	64.425	73.400	88.579	1.00	19.32
ATOM	1985	CA	IMP CYS	331	63.641	74.206	87.649	1.00	20.33
ATOM	1986	C	IMP CYS	331	62.148	73.909	87.498	1.00	21.39
ATOM	1987	O	IMP CYS	331	61.737	72.757	87.342	1.00	22.62
ATOM	1988	CB	IMP CYS	331	64.310	74.200	86.277	1.00	19.26
ATOM	1989	SG	IMP CYS	331	64.038	75.775	85.516	1.00	16.83
ATOM	1990	P	IMP	A1331	71.205	71.206	87.339	1.00	24.40
ATOM	1991	O1P	IMP	A1331	70.381	70.028	86.885	1.00	22.40
ATOM	1992	O2P	IMP	A1331	72.615	71.144	86.864	1.00	18.66
ATOM	1993	O3P	IMP	A1331	71.172	71.333	88.803	1.00	19.75
ATOM	1994	O5*	IMP	A1331	70.688	72.534	86.798	1.00	22.96
ATOM	1995	C5*	IMP	A1331	71.500	73.726	87.024	1.00	14.95
ATOM	1996	C4*	IMP	A1331	71.156	74.601	85.831	1.00	11.32
ATOM	1997	O4*	IMP	A1331	69.758	74.898	85.861	1.00	12.20
ATOM	1998	C3*	IMP	A1331	71.865	75.962	85.934	1.00	12.62
ATOM	1999	O3*	IMP	A1331	73.078	76.011	85.208	1.00	10.24
ATOM	2000	C2*	IMP	A1331	70.883	76.903	85.210	1.00	13.74
ATOM	2001	O2*	IMP	A1331	70.752	76.706	83.816	1.00	11.66
ATOM	2002	C1*	IMP	A1331	69.602	76.308	85.761	1.00	14.52
ATOM	2003	N9	IMP	A1331	68.832	77.205	86.612	1.00	18.13
ATOM	2004	C8	IMP	A1331	69.321	78.030	87.599	1.00	18.02
ATOM	2005	N7	IMP	A1331	68.331	78.568	88.322	1.00	16.06
ATOM	2006	C5	IMP	A1331	67.170	78.093	87.806	1.00	19.77
ATOM	2007	C6	IMP	A1331	65.799	78.289	88.156	1.00	22.26
ATOM	2008	O6	IMP	A1331	65.412	78.995	89.085	1.00	17.37
ATOM	2009	N1	IMP	A1331	64.941	77.579	87.374	1.00	25.96
ATOM	2010	C2	IMP	A1331	65.296	76.706	86.299	1.00	23.29
ATOM	2011	N3	IMP	A1331	66.567	76.524	85.957	1.00	24.20
ATOM	2012	C4	IMP	A1331	67.498	77.200	86.693	1.00	21.15
ATOM	2013	N	ILE	332	61.333	74.959	87.564	1.00	19.04
ATOM	2014	CA	ILE	332	59.899	74.811	87.391	1.00	18.02
ATOM	2015	CB	ILE	332	59.071	75.097	88.696	1.00	16.99
ATOM	2016	CG2	ILE	332	59.423	74.093	89.793	1.00	12.90
ATOM	2017	CG1	ILE	332	59.283	76.525	89.191	1.00	14.79
ATOM	2018	CD1	ILE	332	58.212	77.005	90.159	1.00	8.04
ATOM	2019	C	ILE	332	59.401	75.675	86.226	1.00	20.21
ATOM	2020	O	ILE	332	58.195	75.848	86.050	1.00	21.52
ATOM	2021	N	THR	333	60.330	76.195	85.420	1.00	20.15
ATOM	2022	CA	THR	333	59.993	77.020	84.251	1.00	19.79
ATOM	2023	CB	THR	333	61.287	77.491	83.467	1.00	20.47
ATOM	2024	OG1	THR	333	61.948	78.537	84.191	1.00	18.21
ATOM	2025	CG2	THR	333	60.949	77.996	82.058	1.00	16.88
ATOM	2026	C	THR	333	59.060	76.275	83.281	1.00	18.99
ATOM	2027	O	THR	333	58.124	76.861	82.737	1.00	19.34